

The University of Chicago

PARTIAL SYNTHESIS
OF COMPOUNDS RELATED TO
ADRENAL CORTICAL HORMONES

A DISSERTATION SUBMITTED TO THE FACULTY
OF THE DIVISION OF THE BIOLOGICAL SCIENCES
IN CANDIDACY FOR THE DEGREE OF DOCTOR
OF PHILOSOPHY

DEPARTMENT OF BIOCHEMISTRY
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PREPARATION OF 3(α),11(α)-DIHYDROXY-12-KETOCHOLANIC ACID AND THE PRODUCTS OBTAINED BY WOLFF-KISHNER REDUCTION*

BY VINCENT P. HOLLANDER

The introduction of an oxygen function at C-11 of the steroid nucleus as the first stage in the partial synthesis of adrenal cortical hormones has been the subject of investigation in this and other laboratories for some time. It had been shown that 3(α),11(β)-dihydroxy-12-ketocholanic acid could be successfully reduced to a 3,11-dihydroxychohlanic acid (1, 2) by the Wolff-Kishner method and it was therefore desirable to determine whether the diastereoisomer, 3(α),11(α)-dihydroxy-12-ketocholanic acid, would behave in similar fashion. The latter substance was prepared by low temperature alkaline hydrolysis of methyl 3(α)-acetoxy-11(β)-bromo-12-ketocholanoate (1) in crystalline form and in good yield. The product proved capable of forming ketonic derivatives and upon reduction by the Wolff-Kishner method formed 3(α),11(α)-dihydroxychohlanic acid and Δ^{11} -lithocholenic acid as the principal products. The reaction was therefore similar to the reduction of 3(α),11(β)-dihydroxy-12-ketocholanic acid previously studied by Gallagher and Long (1).

Neither the 3(α),11(α)-dihydroxy-12-ketocholanic acid described in this report nor the 3(α),11(β)-dihydroxy-12-ketocholanic acid described by Long and Gallagher (2) is identical with the compound prepared by Marker and Lawson (3) and formulated by these authors as 3(α),11-dihydroxy-12-ketocholanic acid. It is apparent that the structure of the latter product must be revised; this problem is dealt with in Paper VI (4).

EXPERIMENTAL¹

3(α),11(α)-Dihydroxy-12-ketocholanic Acid—1.004 gm. of methyl 3(α)-acetoxy-11(β)-bromo-12-ketocholanoate, obtained from methyl 3(α)-ace-

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago.

¹ All melting points are corrected. The microanalyses were performed by Mr. John De Lucia (J. De L.), New York, and Professor A. J. Haagen-Smit (A. J. H.-S.), California Institute of Technology. We wish to express our appreciation for this service.

toxy-11,12-epoxycholanate by treatment with hydrobromic acid and subsequent oxidation with CrO_3 , were dissolved in 100 ml. of ethanol, 25.0 ml. of 4.2 N NaOH were added, and the solution was allowed to stand at room temperature for 3 hours. The product was acidified and extracted thoroughly with ether. The ether solution was washed with water, dried with Na_2SO_4 , and evaporated to dryness. The product after two recrystallizations from ethyl acetate melted at $197\text{--}199^\circ$; $[\alpha]_D^{25} = +65.6^\circ$ (absolute ethanol). A mixture with an authentic specimen of the Marker and Lawson acid (m.p. 205° , obtained by vigorous alkaline hydrolysis of methyl 3(α)-acetoxy-11(β)-bromo-12-ketocholanate) (5) melted at 177° .

$\text{C}_{24}\text{H}_{38}\text{O}_5$. Calculated, C 70.90, H 9.42; found (J. De L.), C 70.92, H 9.42

Oxime of 3(α),11(α)-Dihydroxy-12-ketocholanic Acid—226 mg. of 3(α),-11(α)-dihydroxy-12-ketocholanic acid were heated under a reflux with 500 mg. of hydroxylamine hydrochloride and 1 gm. of sodium acetate trihydrate in 10 ml. of ethanol for $2\frac{1}{2}$ hours. The reaction mixture was diluted with water and extracted with ethyl acetate. The ethyl acetate was washed with water and evaporated to dryness. The product crystallized from ethyl acetate-petroleum ether as fine needles and after three recrystallizations melted at $185\text{--}188^\circ$ with decomposition.

$\text{C}_{24}\text{H}_{39}\text{O}_5\text{N}$. Calculated. C 68.37, H 9.32, N 3.32
Found (J. De L.). " 68.25, " 9.29, " 3.24

Methyl 3(α),11(α)-Diacetoxy-12-ketocholanate—621 mg. of 3(α),11(α)-dihydroxy-12-ketocholanic acid were dissolved in 10 ml. of methanol and esterified with diazomethane. As the ester failed to crystallize, the oily product was dissolved in 5 ml. of glacial acetic acid and acetylated² by the addition of 5 ml. of acetic anhydride in the presence of 0.5 ml. of 70 per cent HClO_4 . The solution was chilled in an ice bath and diluted with water, and the ester was extracted with ether. Upon recrystallization from acetone-90-100° petroleum ether the compound formed long, silky needles. After two recrystallizations from the same solvent the product melted at $153\text{--}154^\circ$; $[\alpha]_D^{25} = +38^\circ$ (absolute ethanol).

$\text{C}_{29}\text{H}_{44}\text{O}_7$. Calculated, C 69.02, H 8.79; found (J. De L.), C 68.91, H 8.81

Wolff-Kishner Reduction of 3(α),11(α)-Dihydroxy-12-ketocholanic Acid—6.880 gm. of 3(α),11(α)-dihydroxy-12-ketocholanic acid were dissolved in 5 ml. of absolute ethanol and heated under a reflux for 3 hours with 1.0 ml. of hydrazine hydrate. The alcohol was partially removed under diminished pressure, and the residue dried and transferred to a glass tube with 5.0 ml. of absolute ethanol. 25.0 ml. of sodium ethylate, prepared from 2.36 gm. of

² Schwenk, E., and Whitman, B., personal communication.

sodium, and 0.25 ml. of hydrazine hydrate were added, and the glass tube inserted in a steel bomb and heated at 200° for 90 minutes. The reaction mixture was neutralized and the product separated into soluble and insoluble barium salts by the procedure of Gallagher and Long (1).

Methyl 3(α),11(α)-Dihydroxycholanate—The soluble barium salt was acidified and extracted with ether. 3.698 gm. of acids were obtained, which were esterified with diazomethane and crystallized from ethyl acetate-petroleum ether. 1.077 gm. melting at 93–116° were obtained, which upon recrystallization from the same solvents melted at 133–134°; $[\alpha]_D = +21.7^\circ$ (95 per cent ethanol). There was no depression of the melting point upon admixture with an authentic specimen of methyl 3(α),11(α)-dihydroxycholanate.

$C_{25}H_{42}O_4$. Calculated, C 73.84, H 10.41; found (J. De L.), C 73.53, H 10.73

The product was further characterized by conversion to the diacetate which melted at 116–118° and gave no depression when mixed with an authentic sample of methyl 3(α),11(α)-diacetoxycholanate.

The non-crystalline residue (2.62 gm.) was acetylated and chromatographed twice on Al_2O_3 . 1.413 gm. of crystalline product melting at 112–116° were obtained, which showed no depression of melting point when admixed with an authentic specimen of methyl 3(α),11(α)-diacetoxycholanate. The total yield of 3(α),11(α)-dihydroxycholanate corresponds to 32.6 per cent of theory.

For the purpose of estimating the amount of 3,11,12-trihydroxycholanate acids present in the mixture, advantage was taken of the specific action of lead tetraacetate upon vicinal hydroxyl groups. The dialdehyde produced from the oxidation of the 11,12-glycol was then further oxidized with CrO_3 after protection of the intact hydroxyl at C-3 by acetylation and the amount of acidic product taken as a rough measure of the 3,11,12-trihydroxycholanate acid present in the mixture. The non-crystalline residues from the methyl 3(α),11(α)-diacetoxycholanate were combined, saponified completely, and the acid converted to the methyl ester. The oily product was dissolved in glacial acetic acid and oxidized with lead tetraacetate at room temperature. The reaction consumed approximately 3 equivalents after 72 hours. The reaction product was extracted with ether, dried, and acetylated with acetic anhydride with 0.2 ml. of $HClO_4$ as a catalyst. The acetylated product was oxidized with CrO_3 in glacial acetic acid overnight at room temperature. The neutral fraction was then isolated by extraction with ether and washing with dilute base and with water.

The amorphous neutral residue obtained from 1.15 gm. of acetylated oxidation product weighed 463 mg. and was chromatographed on alumina. 73 mg. of methyl 3(α),11(α)-diacetoxycholanate (m.p. 114–116°, no depres-

sion on admixture with an authentic sample) were obtained. The remainder of the material was oily and could not be crystallized. A control experiment in which the acetylated product was oxidized with CrO_3 without previous oxidation with lead tetraacetate gave an almost quantitative yield of neutral material. These results indicate that about 15 per cent of the soluble barium salt was 3,11,12-trihydroxycholan-ic acid.

Methyl 3(α)-Acetoxy- Δ^{11} -cholenate and Methyl 3(α)-Acetoxycholanate—The insoluble barium salt weighed 2.42 gm. or 32 per cent of theory calculated as the salt of lithocholenic acid. This was acidified, and the acids isolated by extraction with ether were esterified with diazomethane. Acetylation with acetic anhydride and pyridine yielded 2.15 gm. of crystalline product which was separated by the procedure of Seebeck and Reichstein (6). It was dissolved in chloroform and treated with a considerable molar excess of

TABLE I
Separation of Products from Insoluble Barium Salts

Fraction No. (200 ml. each)	Solvent	Ratio	Weight of eluate	Description
			mg.	
1	Petroleum ether		115	Crystalline
2	“ ether-benzene	5:1	180	“
3	“ “	1:1	183	“
4	Benzene		68	Oily
5	Benzene-ether	5:1	45	“
6	Ether		44	“

perbenzoic acid for 16 hours at room temperature. The consumption of perbenzoic acid was almost exactly the theoretical value calculated for methyl lithocholenate. 2.2 gm. of product were obtained. 220 mg. were set aside and the remainder, upon crystallization from acetone and from petroleum ether, yielded 850 mg. of material melting at 144–145°; $[\alpha]_D = +56.4^\circ$ (acetone), $+34.0^\circ$ (toluene). This showed no depression of melting point on admixture with methyl 3(α)-acetoxy-11,12-epoxycholanate. The mother liquors weighed 748 mg. and were chromatographed on 20 gm. of alumina. The fractions shown in Table I were obtained.

Fraction 1 after four recrystallizations from petroleum ether gave 18 mg. of needles, m.p. 130–131°; $[\alpha]_D = +47.4^\circ$ (in 95 per cent ethanol). No depression of the melting point was observed on admixture with methyl 3(α)-acetoxycholanate.

$\text{C}_{27}\text{H}_{44}\text{O}_3$. Calculated, C 74.95, H 10.25; found (A. J. H.-S.), C 75.60, H 10.24

Fractions 2 and 3 were combined and after two recrystallizations from petroleum ether 60 mg. of product melting at 142–144°, $[\alpha]_D = +52.2^\circ$ (acetic acid), were obtained. This compound did not depress the melting point of an authentic sample of methyl 3(α)-acetoxo-11,12-epoxycholanate upon admixture. Fractions 4, 5, and 6 proved difficult to purify and were discarded.

The mother liquors from the recrystallization of Fractions 1, 2, and 3 (270 mg.) were combined and again chromatographed on alumina. Despite careful search and three additional chromatographic separations no substance other than small amounts of methyl 3(α)-acetoxycholanate and methyl 3(α)-acetoxo-11,12-epoxycholanate were obtained.

DISCUSSION

From these experiments and the work of Gallagher and Long (1) it would appear that the configuration of the 11-hydroxyl group in an 11-hydroxy-12-ketosteroid is without influence on the course of the reduction of the carbonyl group to a methylene group by the Wolff-Kishner method. The same products, *i.e.* 3(α),11(α)-dihydroxycholanic acid, 3(α)-hydroxy- Δ^{11} -cholenic acid, small amounts of lithocholic acid, and 3,11,12-trihydroxycholanic acids, are obtained from both the 11(α)- and 11(β)-hydroxy-12-ketocholanic acids. These results substantiate the view that in the course of the Wolff-Kishner reduction at least partial inversion at C-11 invariably occurs in that both diastereoisomers yield the same products. Subsequent to the reduction of the 12-ketonic group, the hydroxyl in the β configuration at C-11 is eliminated with the introduction of a double bond from C-11 to C-12, whereas the 11(α)-hydroxyl group is stable under the experimental conditions. The small amounts of lithocholic acid consistently obtained in the reaction products may be due to reduction of the Δ^{11} -lithocholenic acid by the products of alkaline decomposition of hydrazine.

The findings recorded here would appear to make unnecessary the separation of the insoluble sodium salt of 3(α),11(β)-dihydroxycholanic acid in the procedure of Gallagher and Long (1) for the introduction of the 11-hydroxyl group in the steroid nucleus, since both epimers at C-11 yield the same products. It may be found, however, that despite the slightly higher yield of 3(α),11(α)-dihydroxycholanic acid from 3(α),11(α)-dihydroxy-12-ketocholanic acid the accumulation of side products from the bromination of the 12-ketone may make the separation of the desired product more difficult.

It is likewise apparent from these experiments that 3(α),11(α)-dihydroxy-12-ketocholanic acid is in part converted to 3,11,12-trihydroxycholanic acids in the Wolff-Kishner reduction, since there was a noticeable

reaction with lead tetraacetate in the products remaining after isolation of the major portion of 3(α),11(α)-dihydroxycholanolic acid. These trihydroxy acids are consistently found as products of the Wolff-Kishner reduction of both diastereoisomeric 3(α),11-dihydroxy-12-ketocholanolic acids despite the presence of excess hydrazine in the reaction mixture. Their formation has been discussed in Paper IV (1) of this series. Since the principal object of this investigation was the configuration of the 3,11-dihydroxycholanolic acid formed in the Wolff-Kishner reaction, these side products were not further investigated.

SUMMARY

1. 3(α),11(α)-Dihydroxycholanolic acid was obtained by Wolff-Kishner reduction of 3(α),11(α)-dihydroxy-12-ketocholanolic acid.

2. Lithocholic and Δ^{11} -lithocholenic acids were likewise isolated from the products of reaction.

3. The presence of 3,11,12-trihydroxycholanolic acids in the reaction products was indicated by oxidation with lead tetraacetate.

4. The Wolff-Kishner reduction of 3(α),11(α)-dihydroxy-12-ketocholanolic acid yields qualitatively the same products as that of the 11(β) diastereoisomer.

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PARTIAL SYNTHESIS OF COMPOUNDS RELATED TO ADRENAL CORTICAL HORMONES

DEGRADATION OF THE SIDE CHAIN OF CHOLANIC ACID*

BY VINCENT P. HOLLANDER

The stepwise degradation of the bile acid side chain by the Barbier-Wieland procedure is cumbersome, especially when large amounts of material must be manipulated, and in the majority of instances the yields are far from satisfactory (1-4). Removal of the side chain by oxidation in one step with CrO_3 , as in the familiar degradation of the cholesterol side chain (5), when applied to the bile acids yields very small amounts of etio acid. The neutral products of oxidation are difficult to separate and are likewise obtained in small yield (6).¹ The work recorded here was begun as a model experiment in the hope that a procedure could be devised in which the side chain of the bile acids could be degraded by 2 carbon atoms without the necessity of using the Grignard reaction. Although this end was attained, the yield encountered in the final stages was unexpectedly poor and at the present time it would appear that the method is unsatisfactory for the removal of the side chain of the bile acids. At the completion of this work a preliminary report of the experiments of Jacobsen (7) appeared. The procedure of these authors, using the phenyl ketone instead of the methyl ketone, seems to offer certain advantages which were not achieved in the present work.²

The procedure we have investigated is formulated in the accompanying diagram. Several complications were encountered. The bromo ketone (VI) proved to be difficult to purify. Whether this is caused by traces of 25-bromo ketone or by the presence of the two possible epimeric 23-bromo ketones has not been decided. The dehydrobromination of VI was possible

* The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of Chicago.

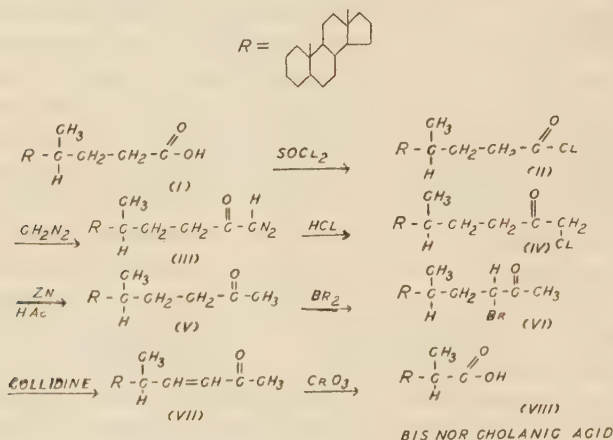
¹ Personal communications from other members of the group and unpublished experiments from this laboratory.

² The promising procedures of Meystre, Frey, Wettstein, and Miescher (8) and of Meystre, Ehmann, Neher, and Miescher (9) were received while this manuscript was in press.

with boiling collidine but the α,β -unsaturated ketone was obtained only as an oil. The oxidation of VII by CrO_3 gave poor yields of VIII. The characterization of the final product was difficult because of the several isomeric bisnorcholanic acids described in the literature (1).

EXPERIMENTAL³

25-Chloromethyl Norcholanyl Ketone (IV)—9.0 gm. of cholanic acid (I) were dissolved in 25 ml. of thionyl chloride purified by the procedure of Glattfeld and Kribben (10) and the solution allowed to stand at room temperature for 4 hours. The excess thionyl chloride was distilled under diminished pressure on the steam bath and the removal completed by the distillation of fresh portions of benzene from the crystalline mass. The



acid chloride was dissolved in 100 ml. of benzene and with continuous stirring and cooling to -10° added dropwise to a large excess of ethereal diazomethane, previously dried with sodium wire. The reaction mixture stood overnight, during which time the temperature was permitted to rise to that of the room. The diazo ketone failed to crystallize readily and even after chromatographing 1.08 gm. on Al_2O_3 no crystalline product was obtained. The remainder of the diazo ketone was therefore treated with 300 ml. of a 3.5 N solution of hydrogen chloride in anhydrous ether and the reaction mixture allowed to stand for 10 minutes. The ether was washed

³ All melting points are corrected. The microanalyses were performed by Dr. Joseph Alicino (J. A.), The Squibb Institute for Medical Research, New Brunswick, New Jersey, and Mr. John De Lucia (J. De L.), New York, Dr. T. S. Ma (T. S. M.), Department of Chemistry of the University of Chicago, and Professor A. J. Haagen-Smit (A. J. H.-S.), California Institute of Technology. We wish to express our appreciation for this service.

with dilute Na_2CO_3 solution and with water, dried over Na_2SO_4 , and the ether removed. 9.0 gm. of crude crystalline product were obtained. This was purified by chromatographing on 60 gm. of Al_2O_3 and 6.1 gm. of product obtained which after two recrystallizations from methanol and from acetone gave needles with a melting point of $109\text{--}110^\circ$; $[\alpha]_D^{25} = +21.7^\circ$ (CHCl_3).

$\text{C}_{25}\text{H}_{41}\text{OCl}$. Calculated. C 76.40, H 10.51, Cl 9.02
Found (J. A.). " 76.29, " 10.51, " 9.41

Norcholanyl Methyl Ketone—4.1 gm. of slightly impure 25-chloromethyl norcholanyl ketone were dissolved in 20 ml. of glacial acetic acid, 10 gm. of granulated zinc added, and the mixture heated under a reflux for 2 hours. The solution was cooled, ether added, and the zinc removed by decantation. The ether solution was extracted with NaHCO_3 solution and with water and the ether removed. 3.6 gm. of crude product were obtained, which was purified by chromatographic adsorption on Al_2O_3 . 1.98 gm. of analytically pure material were obtained together with smaller quantities of colored crystalline product which were discarded. Recrystallized from acetone and from methanol the compound formed long thin needles, m.p. $114\text{--}115^\circ$; $[\alpha]_D^{27} = +22.5^\circ$ (CHCl_3).

$\text{C}_{26}\text{H}_{42}\text{O}$. Calculated, C 83.73, H 11.78; found (J. A.), C 83.30, H 11.64

23-Bromonorcholanyl Methyl Ketone—1.65 gm. of norcholanyl methyl ketone were dissolved in 50 ml. of glacial acetic acid, and 15.2 ml. of 0.130 N Br_2 in glacial acetic acid and 2 drops of 48 per cent aqueous hydrobromic acid added. After 1 hour the reaction mixture was diluted with water and extracted with ether. The ether solution was washed with NaHCO_3 solution and with water and the ether removed. The residue was purified by chromatographic adsorption on alumina.⁴ 1.97 gm. of a light oil were

⁴ In earlier experiments with this substance and 25-bromomethyl norcholanyl ketone chromatographic adsorption had been used in purification. Considerable difficulty was experienced in obtaining satisfactorily pure preparations and the halogen values were invariably low. Mr. W. Saschek, Department of Biochemistry, Columbia University, called our attention to his observation that the silver halide precipitate obtained in his microanalysis appeared to be silver chloride rather than silver bromide; analysis of the silver salt confirmed this observation. We were at that time using an alumina which had been extracted with 10 per cent hydrochloric acid and subsequently washed twenty times with distilled water. Although the final seven washings were neutral, the alumina still contained considerable chloride ion. An exchange reaction apparently occurred on the column. This possibility is of importance when sensitive substances are chromatographed. We have since substituted acetic acid in the extraction of base from commercial alumina and have not experienced any similar difficulty. We should like to express our appreciation for the assistance of Mr. Saschek.

eluted with 60–70° petroleum ether and crystallized from methanol. It proved difficult to obtain a product with a sharp melting point and seven crystallizations were required before long needles of constant melting point, 94.5–95.5°, were obtained; $[\alpha]_D^{28} = +86.8^\circ$ (CHCl_3).

$\text{C}_{25}\text{H}_{41}\text{OBr}$. Calculated. C 68.63, H 9.45, Br 18.27
Found (T. S. M.). " 69.09, " 9.05, " 18.37

Methyl Bisnorcholanate and Bisnorcholanic Acid—2.38 gm. of 23-bromonorcholan-20-yl methyl ketone were heated under a reflux for 4 hours with 5.0 ml. of redistilled collidine. After cooling, ether was added and the solution washed with dilute HCl and with water, and the ether removed. The dark gummy residue was dissolved in petroleum ether and chromatographed over 30 gm. of alumina. The eluate from 500 ml. of petroleum ether consisted of 1.20 gm. of a light yellow oil. Attempts to crystallize this product were unavailing. It was dissolved in 45 ml. of glacial acetic acid, 50 ml. of 1.36 N CrO_3 were added, and the mixture was allowed to stand for 18 hours at room temperature. The excess CrO_3 was destroyed by the addition of methanol and the product separated into acid and neutral fractions. The neutral fraction weighed 517 mg. The acid fraction (174 mg.) was esterified with diazomethane and purified by chromatographic separation on alumina. 29 mg. of feathery crystals were obtained which upon recrystallization from ethanol melted at 115–117°; $[\alpha]_D^{26} = +22.6^\circ$ (CHCl_3); $[\alpha]_D^{28} = +21.4^\circ$ (95 per cent ethanol).

$\text{C}_{23}\text{H}_{38}\text{O}_2$. Calculated, C 79.83, H 11.07; found (J. De L.), C 79.32, H 11.15

The methyl ester was saponified with 0.05 N alcoholic NaOH under a reflux and the acid obtained crystallized from petroleum ether as small prisms, m.p. 171–175°; $[\alpha]_D = +10^\circ$ (95 per cent ethanol). For the ϵ isomer of bisnordesoxycholic acid Wieland, Schlichting, and Jacobi (1) report the melting point of the free acid as 181°, $[\alpha]_D^{27} = +14^\circ$, and the methyl ester melting point 117°.

In a subsequent experiment isolation of the bisnorcholanic acid was achieved by preliminary saponification of the methyl esters of the acidic fraction with alcoholic base at room temperature, since methyl bisnorcholanate is saponified with difficulty under these conditions. 674 mg. of acids were esterified with diazomethane. The product was dissolved in 15 ml. of 95 per cent ethanol; 1.0 ml. of 3.2 N NaOH was added and the solution allowed to stand at room temperature for 2 hours. 341 mg. of unhydrolyzed esters were obtained. These were completely hydrolyzed by heating under a reflux with alcoholic base and the acids isolated. 161 mg. were obtained which crystallized poorly from petroleum ether. The product was esterified with diazomethane and the ester recrystallized from

ethanol as needles, m.p. 65–66°; $[\alpha]_D^{25} = +9.1^\circ$ (chloroform); $+30.3^\circ$ (ethanol).

$C_{23}H_{38}O_2$. Calculated, C 79.83, H 11.07; found (A. J. H.-S.), C 79.97, H 11.04

The methyl ester was saponified with 0.05 N NaOH under a reflux and the acid obtained melted at 196–201°; $[\alpha]_D^{25} = +19.5^\circ$ (ethanol). Wieland, Schlichting, and Jacobi (1) report the melting point of the β isomer of bisnorcholanic acid as 242°, $[\alpha]_D^{25} = +23^\circ$, and the methyl ester of this isomer as an oil.

SUMMARY

A procedure for the degradation of the bile acid side chain by the elimination of 2 carbon atoms has been described. Cholanic acid was converted to norcholanyl methyl ketone, brominated at C-23, and the elements of HBr removed with collidine. Oxidation by CrO_3 yielded two isomers of bisnorcholanic acid.

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